PATENT COOPERATION TREATY

10/088677

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SMWBP5881735		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03601	20/09/2000	21/09/1999
Applicant		
ISIS INNOVATION LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT [redacted] 00/03601

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/30 A61K39/00 A61K39/015

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, WPI Data, PAJ, EPO-Internal, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAZANJI MIRDAD ET AL: "Expression and immunogenicity in rats of recombinant adenovirus 5 DNA plasmids and vaccinia virus containing the HTLV-I env gene." INTERNATIONAL JOURNAL OF CANCER, vol. 71, no. 2, 1997, pages 300-307, XP000982098 ISSN: 0020-7136	1,2, 5-11, 14-16
Y	page 300, paragraph 1 page 300, paragraph 7 page 301; table 1A page 301, paragraph 6 - paragraph 8 page 302; figure 1 page 300, paragraph 9 -page 301, paragraph 2 page 302, paragraph 9 -page 303, paragraph 4 page 303, paragraph 5 -/--	3,4,12, 13

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2001	11/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sitch, W

8

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
	page 303, paragraph 8 ---	
Y	GILBERT SARAH C ET AL: "A protein particle vaccine containing multiple malaria epitopes." NATURE BIOTECHNOLOGY, vol. 15, no. 12, 1997, pages 1280-1283, XP002164101 ISSN: 1087-0156 cited in the application page 1282, paragraph 5 -page 1283, paragraph 3 ---	3,12
Y	HANKE T ET AL: "Immunogenicities of intravenous and intramuscular administration of modified vaccinia virus Ankara-based multi-CTL epitope vaccine for human immunodeficiency virus type 1 in mice." JOURNAL OF GENERAL VIROLOGY, vol. 79, no. 1, January 1998 (1998-01), pages 83-90, XP002164102 ISSN: 0022-1317 'Discussion' page 87 -page 88 ---	4,13
A	NATUK ROBERT ET AL: "Immunogenicity of recombinant human adenovirus-human immunodeficiency virus vaccines in chimpanzees." AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 9, no. 5, 1993, pages 395-404, XP000979583 ISSN: 0889-2229 page 397; table 1 page 401; figure 1 ---	5,6,14
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996 WARNIER GUY ET AL: "Induction of a cytolytic T-cell response in mice with a recombinant adenovirus coding for tumor antigen P815A." Database accession no. PREV199699138086 XP002164103 abstract & INTERNATIONAL JOURNAL OF CANCER, vol. 67, no. 2, 1996, pages 303-310, ISSN: 0020-7136 --- -/--	7,15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SCHNEIDER JORG ET AL: "Enhanced immunogenicity for CD8+ T cell induction and complete protective efficacy of malaria DNA vaccination by boosting with modified vaccinia virus Ankara." NATURE MEDICINE, vol. 4, no. 4, April 1998 (1998-04), pages 397-402, XP000739989 ISSN: 1078-8956 cited in the application page 398; table 1	

CLAIMS

1. Use of a replication-deficient adenoviral vector encoding an antigen or a CD8+ T cell epitope of said antigen, in the manufacture of a medicament for treating an individual in which a CD8+ T cell immune response to the antigen is of therapeutic or prophylactic benefit, wherein the medicament is for administration to such an individual to boost in the individual a CD8+ T cell immune response to the antigen following prior administration of a priming composition comprising said antigen or epitope or nucleic acid encoding said antigen or epitope.

2. Use according to claim 1 wherein the priming composition comprises DNA encoding said antigen or epitope.

3. Use according to claim 1 wherein the priming composition comprises recombinant Ty-VLP

4. Use according to claim 1 wherein the priming composition comprises Modified Virus Ankara (MVA).

5. Use according to any one of claims 1 to 4 wherein the medicament is a boosting composition for administration prior to administration of another, different boosting composition comprising said antigen or epitope.

6. Use according to any one of claims 1 to 4 wherein the medicament is a boosting composition for administration following administration of another, different boosting comprising said antigen or epitope.

7. Use according to any one of claims 1 to 6 wherein the medicament is for intradermal administration.

8. Use according to any one of claims 1 to 6 wherein the medicament is for intramuscular administration.

9. A method of boosting a CD8+ T cell immune response to an antigen in an individual, the method including provision in the individual of a replication-deficient adenoviral vector including nucleic acid encoding the antigen or a CD8+ T cell epitope of said antigen operably linked to regulatory sequences for production of said antigen or epitope in the individual by expression from the nucleic acid, whereby a CD8+ T cell immune response to the antigen previously primed in the individual is boosted.

10. A method of inducing a CD8+ T cell immune response to an antigen in an individual, the method comprising administering to the individual a priming composition comprising the antigen or a CD8+ T cell epitope of said antigen or nucleic acid encoding said antigen or epitope and then administering a

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMWBP5881735		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03601	20/09/2000	21/09/1999
International Patent Classification (IPC) or national classification and IPC A61K39/00		
Applicant ISIS INNOVATION LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/04/2001	14.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Sitch, W Telephone No. +31 70 340 3040

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03601

I. Basis f the r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-25	as originally filed				

Claims, No.:

10-16	as originally filed				
1-9	as received on	05/11/2001	with letter of	05/11/2001	

Drawings, No.:

1-3	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 9-16 with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 12-15
	No:	Claims	10, 11, 16
Inventive step (IS)	Yes:	Claims	1-9, 12-15
	No:	Claims	10, 11, 16
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

The comments of the applicant during these proceedings have been taken into account.

Reference is made to the following documents:
D1: Int. J. Cancer, 71, 1997, 300-307
D2: Nature Medicine, vol. 4, 1998, 397-402.

1. Novelty (Art. 33(2) PCT).

1.1 Claim 10 relates to a method of inducing a CD8+ T cell immune response by administering a priming composition comprising an antigen or CD8+ T cell epitope thereof, or nucleic acid encoding the same, and then administering a boosting composition comprising a replication deficient adenoviral vector including nucleic acid encoding said antigen or epitope.

1.2 D1 addresses the provision of a vaccine against HTLV-1 (page 300, para. 1). Two immunisation protocols expected to induce cell-mediated and antibody responses in vaccinees were utilised for vaccinating against the agent (page 300, para. 7). As indicated in table 1A, page 301, and page 301, paras. 6-8, in one protocol, WKY rats received intramuscular Ad5-HTLV-1-env, followed by boosting with Ad5-HTLV-1-gp46. (The constructs used for producing the viral vectors delivered are detailed in fig. 1, page 302. The skilled person would clearly realise that the vectors obtained using such constructs, whereby said constructs, comprising essentially only the ITR, encapsidation sequences, major late promoter of Ad5 associated with the tripartite leader sequence,

and a Ad pIX peptide coding sequence, are replication defective. Production of viral vectors is achieved using 293 helper cells (page 300, para. 9 - page 301, para. 2)). The nature of the immune response to the delivered antigens is elaborated at page 302, para. 9 - page 303, para. 4. Of note as regards the present application, in the protocol referred to above, a CTL response was clearly generated against the delivered antigen, and the skilled person would be aware that such a response is in all likelihood CD8+ T cell mediated. The susceptibility to infection by HTLV-1 of WKY rats immunised using this protocol was investigated by injecting them with MT-2 cells (page 303, para. 5). Provirus is stated not to have been detected in certain of the immunised rats, including those primed with Ad5-HLV-1-env and boosted with Ad5-HTV-1-gp46 (page 303, para. 8), indicating a protective effect against challenge in such vaccinees.

D1 thus discloses subject matter falling within the scope of claims 10, 11 and 16, the subject matter of which therefore lacks novelty.

2. Inventive Step (Art. 33(3) PCT)

2.1 Upon consideration of the technical effects demonstrated in the present application, the closest prior art for the assessment of inventive step is considered to be D2. D2 relates to the provision of means for enhancing the CD8+ T cell response in a malaria DNA vaccine. Priming with plasmid DNA encoding a pre-erythrocytic antigen of Plasmodium berghei followed by a boost with recombinant modified vaccinia virus Ankara expressing the same antigen produced a high level peptide specific CD8+ T cell response, and provided complete protection against subsequent P. berghei sporozite challenge (see page 397 for summary of protocol and results achieved, and page 398, table 1).

Essential difference between claim 1 and D2, protocol for inducing a CD8+ type protective immune response involves boosting with an adenoviral vector encoding antigen.

Objective problem in light of D2: provision of alternative means of inducing a protective CD8+ T cell response in an individual in an immunisation protocol, and whereby a highly protective immune response against subsequent challenge is achieved.

2.2 In consideration of the available prior art, and in view of the knowledge of the man

skilled in the art, there would appear no motivation or indication for the skilled person to attempt to solve the objective problem addressed by the present application in the way as provided by claim 1. Accordingly, inventive step for claim 1, and in addition claims 2-9 and 12-15, may thus be recognised.

3. For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

PATENT COOPERATION TREATY

RECEIVED
11 APR 2001

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
MEWBURN ELLIS
Attn. WALTON, S.
York House
23 Kingsway
London WC2B 6HP
UNITED KINGDOM

Applicant's or agent's file reference SMWBP5881735	Date of mailing *(day/month/year)* 11/04/2001
International application No. PCT/GB 00/03601	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant ISIS INNOVATION LIMITED et al.	International filing date *(day/month/year)* 20/09/2000

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Geertruida Groeneveld-Van der Spek

NOTE FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/03601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.